

Oral Antipyretic Therapy

Evaluation of Aspirin-Acetaminophen Combination

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A combination of aspirin and acetaminophen was compared to either oral antipyretic agent used alone to reduce fever in children in a controlled clinical study of 60 outpatients and 60 inpatients between the ages of 6 months and 5 years with rectal temperatures greater than 38.9 C (102 F). Temperatures were recorded at one, two, three, four, and six hours after administration of treatment. Results were similar for outpatients and inpatients. The antipyretic combination was generally superior to either drug used alone with average temperature differences reaching statistical significance at many time intervals. Rate and degree of temperature reduction were not greater but were more sustained. Treatment with this combination appears rational in children with high fever when a sustained antipyretic effect is desired. Repeated administration at six-hour intervals lessens the need for more frequent administration of aspirin alone to treat fever.

It is not clear whether fever itself is beneficial or detrimental to the outcome of acute infectious diseases.¹ Most pediatricians, however, treat fever per se if it is excessively

high in order to relieve discomfort and to lessen the probability of febrile convulsions in susceptible children. Orally administered antipyretic drugs, sponging with various solutions, or both in combination are the methods most commonly employed.²

Aspirin and acetaminophen are the most frequently used oral antipyretic agents. Clinical studies have shown that both are effective in reducing fever, but no statistically significant difference in their antipyretic effect has been demonstrated.^{3,4} Increasing the dose of aspirin or acetaminophen above that usually recommended has not resulted in a better or more sustained antipyretic effect.⁵ However, we have observed an apparent additive effect when aspirin and acetaminophen are used in combination to reduce fever. The present clinical study was undertaken to test this observation.

Materials and Methods

The study was conducted during the period from September to December 1970. Study patients consisted of 120 children between the ages of 6 months and 5 years who presented with febrile illnesses of less than three days' duration and rectal temperatures of 38.9 C (102 F) or above. Those who had received antipyretic medication within four hours of the initial examination were excluded. Study patients were composed of two groups that were evaluated separately; half were patients who had been hospitalized because of their illness and the other half were treated as outpatients.

Children fulfilling these criteria were assigned to one of three treatment groups; group A received aspirin, group B, acetaminophen; and group C, a combination of aspirin and acetaminophen. The dosage of each medication is listed in the Table.

The type of treatment each patient received was determined by opening the next in order of a series of numbered envelopes, each of which contained a card in-

Antipyretic Dosage			
Age, mo	Group A (Aspirin)*	Group B (Acetaminophen)†	Group C (Aspirin and Acetaminophen)
6-18	One tablet	0.8 ml	One tablet aspirin 0.8 ml acetaminophen
18-30	Two tablets	1.6 ml	Two tablets aspirin 1.6 ml acetaminophen
30-48	Three tablets	2.4 ml	Three tablets aspirin 2.4 ml acetaminophen
48-60	Four tablets	3.2 ml	Four tablets aspirin 3.2 ml acetaminophen

* Aspirin: one tablet = 75 mg.

† Acetaminophen: 0.8 ml = 80 mg.

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dicating the type of treatment to be given. The treatment groups were randomized in the envelopes so that each was used equally. There were 60 envelopes for outpatients and 60 for inpatients and in each there were 20 envelopes assigning patients to group A, 20 for group B, and 20 for group C. A nurse administered the appropriate medication and recorded the treatment group; the investigators did not know what type of treatment any child received until termination of the study.

The children were examined to determine the cause of fever and this along with other pertinent clinical data was recorded. Rectal temperatures were obtained with a standard mercury thermometer which was placed to a depth of 2.5 cm in the rectum and read after three minutes. Temperatures were recorded on all patients prior to treatment and at one, two, three, four, and six hours after receiving their medications. Hospitalized patients had their temperatures taken by a nurse while the child's mother took the temperature of those children treated as outpatients. Aside from the differences in antipyretic medication, all study patients received the same general treatment and there was no significant variation in physical or environmental factors.

Results

The treatment groups were comparable with respect to age, sex, etiology of fever, and duration of fever prior to and following treatment. The etiology of fever in outpatients was shown to be due to otitis media, 32%; viral upper-respiratory tract infection, 27%; pneumonia, 7%; urinary tract infection, 3%; unknown, 17%; and other, 14%. The cause of fever in inpatients was shown to be due to pneumonia, 33%; otitis media, 15%; croup, 12%; cellulitis, 8%; infectious diarrhea, 5%; unknown, 15%; and other, 12%. Medications were retained by all patients. Fluids were offered ad lib and intake was similar in all study groups. No signs of drug toxicity or untoward reactions were observed in any of the patients. A similar percentage of children in each of the three study groups received antimicrobial therapy.

Figures 1 and 2 show the results ob-

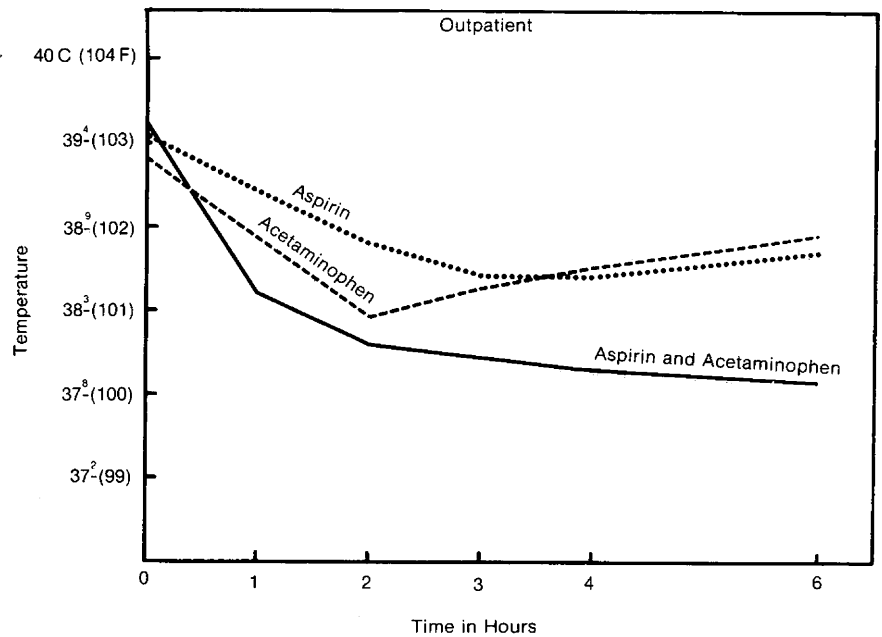


Fig 1.—Vertical axis indicates temperature both in centigrade and Fahrenheit, and the horizontal axis indicates time in hours after initiation of treatment. Superscript numbers indicate tenths of a degree of temperature.

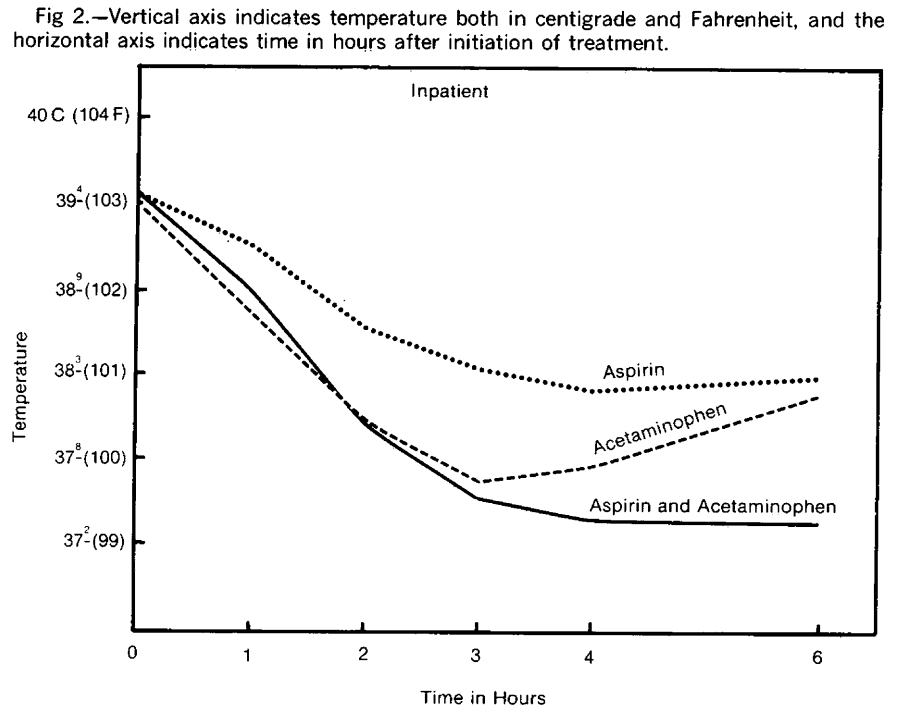


Fig 2.—Vertical axis indicates temperature both in centigrade and Fahrenheit, and the horizontal axis indicates time in hours after initiation of treatment.

tained in outpatients and inpatients, respectively. The temperature curve of each treatment group was obtained by averaging the temperatures of patients within that group before initiation of treatment and at the various time intervals indicated thereafter. The average temperature before treatment in all study groups in both outpatients and inpatients were remarkably similar.

Pair-wise comparisons were made for each treatment regimen at each time point after initiation of therapy with the Mann-Whitney nonparametric test⁶ and with 5% significant levels based on Duncan's multiple range test.⁷ In outpatients, the combination of aspirin and acetaminophen was significantly superior to aspirin alone at one, two, three, and four hours ($P < .05$). At six hours the difference approached but did not reach statistical significance ($P = .052$). In inpatients, the combination was significantly superior to aspirin alone at two, three, four, and six hours ($P < .02$). The combination was statistically more effective than acetaminophen alone at three and four hours in outpatients only ($P < .05$).

Acetaminophen alone was significantly superior to aspirin alone at one and two hours in outpatients ($P < .05$) and at two and three hours in inpatients ($P < .01$) but in neither group was there a sustained reduction in fever as was seen with the aspirin-acetaminophen combination. Minor differences in the temperature curves of patients of the same treatment group occurred in outpatients

when compared to inpatients, but these differences were not significant.

Comment

The present study has shown that a combination of aspirin and acetaminophen is more effective in reducing fever in children than either drug used alone. The rate and degree of temperature reduction is not greater with the combination of drugs but it is significantly more sustained. The mechanism responsible for this effect is not readily apparent. Both drugs are felt to produce their antipyretic effect centrally by their action on the thermoregulatory center of the hypothalamus.⁵ Heat loss in the febrile patient is then produced secondarily by peripheral vascular dilatation and sweating. It may be that one of these drugs actually potentiates the action of the other at this site or the enhanced antipyretic effect achieved by the two drugs used in combination may be mediated through some other mechanism.

Both aspirin and acetaminophen are detoxified and excreted by similar processes. The possibility that they may compete with one another in this way and cause accumulation in the tissues of one or both drugs seems rational. If serum salicylate levels in patients treated with combined aspirin-acetaminophen therapy were found to be greater than those receiving aspirin alone at a time when the added effect of the combined drug regimen was most apparent, this possibility would seem plausible. Actually, serum salicylate levels taken

from a number of children four hours after receiving aspirin-acetaminophen or aspirin alone were all quite similar. In addition, it is known that either of these drugs taken in excess of the regular therapeutic dose does not result in an enhanced antipyretic effect. Aspirin in excess may, in fact, induce fever.⁵ These observations would suggest that the enhanced antipyretic effect produced by the aspirin-acetaminophen drug combination is not produced by higher or more sustained blood levels of either drug as a consequence of competition for detoxification and excretion.

No signs of drug intolerance or toxicity were observed in the 20 outpatients and 20 inpatients receiving combined aspirin and acetaminophen therapy. Only a single dose of each medication was given to these study patients; however, we have administered both drugs together to many patients repeatedly without evidence of drug toxicity. At present we do not have sufficient information to recommend that this drug combination can be given repeatedly for extended periods of time without toxic reaction.

The more sustained reduction in fever noted in those patients receiving the aspirin-acetaminophen combination suggests that treatment with this regimen does not need to be repeated as often as when either of these drugs is used alone. Combined aspirin-acetaminophen given every six hours actually results in less aspirin being given over a period of time since it is usually necessary to give aspirin every four hours for control of fever.

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